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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,802	07/22/2003	Martin C. M. M. Barnardo	1181-282	5302

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,802	BARNARDO ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed April 21, 2006 is acknowledged and has been entered.

Specification

1. The disclosure is objected to because of the following informalities: the disclosure does not provide a section briefly describing the drawings.

Appropriate correction is required.

Note: this objection was made in the previous office action. See first paragraph on page 3 of the previous office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 8, lines 13-20 and page 13, lines 19-23 and various other places in the specification applicant discloses that recombinant MHC or MHC-type molecule is used in the method of the invention. On page 9, lines 15-23 in the specification. The applicant discloses functionally equivalent variants, derivatives or fragments refer to MHC molecules related to or derived from naturally

occurring MHC molecules wherein the amino acid sequence of one or more components of said MHC molecules (e.g. the class I heavy chain, class II) has been modified by single or multiple amino acid (e.g. at 1 to 50, e.g. 10 to 30, preferably 1 to 5 bases) substitution, addition and/or deletion but which nonetheless retains functional activity. On page 10, lines 7-13 in the specification. The applicant discloses that the derivatives and variants are closely related to one or more components of the naturally occurring MHC molecules, e.g. are encoded by nucleic acid molecules with more that 70%, preferably more than 80, 90 or 95% sequence identity to naturally occurring sequences or exhibit such sequence identity to the functional portions of these sequences. Further, on page 11, line 27- page 12, line 3 the applicant discloses the fragments may be derived from naturally occurring molecules or from functionally equivalent variants or derivatives thereof. Preferably the fragments are between 50 and 500 residues, e.g. 100 and 250 residues in length. The applicant does not disclose all recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof. Further, the applicant does not disclose the nucleic acid sequence encoding the variants, which is required. Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the

claimed genus. At section B(1), the court states that "An adequate written description of a DNA... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere which or plan for obtaining the claimed chemical invention". Applicant has not disclosed any examples of recombinant MHC type or recombinant HLA type molecules nor provided any definition for MHC type or recombinant HLA type molecules.

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid sequence encoding the variants is required. See *Fiers v. Revel,* 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.,* 18 USPQ2d 1016.

4. Claims 22-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant MHC monomers, known allelic variants and specific peptides, does not reasonably provide enablement for all recombinant MHC molecules or functionally equivalent recombinant variants, derivative or fragments thereof or recombinant MHC type molecules or recombinant HLA type molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be

considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to a method of depleting a sample of MHC or HLA molecule antibodies comprising contacting the sample with recombinant MHC or recombinant MHC-type or HLA-type molecules are sufficiently antigenic to be bound by anti-MHC antibodies in the sample; and removing the bound anti-MHC antibodies from the sample, whereby the sample has been depleted of anti-MHC antibodies. The specification on page 5, lines 9-10 and page 17 discloses recombinant MHC monomers. The applicant discloses MHC-type and HLA-type molecues can be used and that functionally equivalent variants, derivatives or fragments refer to MHC molecules related to or derived from naturally occurring MHC molecules wherein the amino acid sequence of one or more components of said MHC molecules (e.g. the class I heavy chain, class II) has been modified by single or multiple amino acid (e.g. at 1 to 50, e.g. 10 to 30, preferably 1 to 5 bases) substitution, addition and/or deletion but which nonetheless retains functional activity. On page 10, lines 7-13 in the specification. The applicant discloses that the derivatives and variants are closely related to one or more components of the naturally occurring MHC molecules, e.g. are encoded by nucleic acid molecules with more that 70%, preferably more than 80, 90 or 95% sequence identity to naturally occurring sequences or exhibit such sequence identity to the functional portions of these sequences. Further, on page 11, line 27 – page 12, line 3 the applicant

discloses the fragments may be derived from naturally occurring molecules or from functionally equivalent variants or derivatives thereof. Preferably the fragments are between 50 and 500 residues, e.g. 100 and 250 residues in length. The applicant does not disclose all recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof to detect anti MHC or anti HLA antibodies. It is possible the combinations of variants, derivatives or fragments thereof may lose their functionality and thus would not work to detect the antibodies.

The working examples in the specification are directed to recombinant monomers HLA-A2 and HLA-B8. At best, the binding of the HLA antibodies can be determined only by using recombinant monomers or known allelic variants. There is no guidance in the specification disclosing which MHC-type molecules, HLA-type molecules, derivatives, variants, fragments or combinations thereof, which can be used for the depletion of MHC molecule antibodies. Further, Applicant has not provided any examples of recombinant MHC type or recombinant HLA type molecules nor provided any definition for MHC type or recombinant HLA type molecules. Such is not seen as sufficient to support the breath of the claims and one skilled in the art cannot practice the claimed invention without undue experimentation, because in order to deplete the anti-MHC antibodies one skilled in the art would have to perform experiments to determine which MHC-type molecules, HLA-type molecules variants, derivatives or fragments did or did not function to bind to the anti-MHC antibodies.

5. Claims 29, 33, 41 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 10, lines 7-13 in the specification. The applicant discloses the derivatives and variants are closely related to one or more components of the naturally occurring MHC molecules, e.g. are encoded by nucleic acid molecules with more than 70%, preferably more than 80, 90 or 95% sequence identity to naturally occurring sequences or exhibit such sequence identity to the functional portions of these sequences. The applicant does not disclose that the folding peptide comprises an amino acid sequence at least 80% identical to the amino acid sequence consisting of SEQ ID NO:2 – SEQ ID NO:8. There is no description in the specification disclosing the folding peptide comprises an amino acid sequence at least 80% identical to the amino acid sequence consisting of SEQ ID NO:2 – SEQ ID NO:8.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 22-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 the recitation "recombinant MHC-type molecules" is vague and indefinite. It is unclear what applicant intends. Applicant has not provided a definition for the term and it is unclear what is considered to be a MHC-type molecule. See deficiencies throughout the claims.

Claim 22, line 5 the recitation "sufficiently antigenic to be bound" is vague and indefinite. First, it is unclear what is considered to be sufficient. Second, the recitation is not a positive recitation and it appears that in order for the method to work that the recombinant molecule must bind to the antibodies in order to remove the antibodies from the sample. See also deficiencies found in claim 36.

Claim 36 the recitation "recombinant HLA-type molecules" is vague and indefinite. It is unclear what applicant intends. Applicant has not provided a definition for the term and it is unclear what is considered to be a HLA-type molecule. See deficiencies throughout the claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 22-26, 34, 36-38 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeVito et al., (Adsorption of cytotoxic Anti-HLA antibodies with HLA Class I Immunosorbant Beads, Transplantation, Vol. 49, 925-931, No. 5, May 1990) in view of Walter et al. (Stimulation of human cytotoxic T cells with HIV-1 derived peptides presented by recombinant HLA-A2 peptide complexes, International Immunology, Vol. 9, No. 3, pp.451-459).

DeVito et al disclose methods of depleting a sample of anti-HLA antibodies. DeVito et al disclose contacting a patients sera containing anti-HLA antibodies with beads which comprise immobilized HLA (p. 927). DeVito et al disclose incubating the sample and beads and allowing binding to occur and separating the beads from the sera after centrifugation. DeVito teaches that recombinant technology may be used to produce the HLA antigen to be used in the assays (p. 925).

DeVito et al differ from the instant invention in failing to specifically teach the use of a recombinant HLA in the method.

Walter et al teach recombinant HLA-A2 peptide complexes bound to beads. Walter et al teach that the recombinant HLA-A2 peptide binds to anti-HLA antibodies.

Walter et al teach that the E.coli system and the subsequent refolding provides an abundant source of homogenous HLA-peptide complexes and the recombinant soluble complexes provide for new tools for exploring diverse problems and issues (p. 458).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate recombinant HLA-A2 complexes as taught by Walter et al into the method of DeVito et al because DeVito et al specifically teaches that recombinant technology may be used to produce the HLA antigen and Walter et al teaches that the E.coli system and the subsequent refolding provides an abundant source of homogenous HLA-peptide complexes and also provides for new tools for exploring diverse problems and issues.

12. Claims 22-29, 34, 36-41 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeVito et al., (Adsorption of cytotoxic Anti-HLA antibodies with HLA Class I Immunosorbant Beads, Transplantation, Vol. 49, 925-931, No. 5, May 1990) in view of Barnardo et al (Detection of HLA antibodies using single recombinant HLA alleles, Human Immunology, Abstracts 1999, Volume 60, Supplement 2) or Barnardo et al (Detection of HLA-Specific IgG using single, recombinant HLA alleles, Human Immunology (1999) Vol 60., No. Suppl. 1, pp. S1.

See above for the teachings of DeVito et al.

DeVito et al differ from the instant invention in failing to specifically teach recombinant HLA molecules for binding the anti-HLA antibodies.

Barnardo et al (Abstracts 1999) & (Human Immunology 1999) teach the use of recombinant HLA monomer molecules bound to microspheres to bind to anti-HLA antibodies in a sample.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate recombinant HLA molecules as taught by Barnardo et al into the method of DeVito et al because DeVito et al specifically teaches that recombinant technology may be used to produce the HLA antigen and Barnardo et al shows that recombinant HLA molecules specifically bind to anti-HLA antibodies. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating recombinant HLA molecules as taught by Barnardo et al into the method of DeVito et al.

13. Claims 22-27, 30, 31, 34-39, 42, 43 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hildebrand et al. (US 2003/0166057) in view of Whitehead et al (US 4,554,088) and DeVito et al (Transplantation Vol 49 No.5 1990, pages 925-931).

Hildebrand et al disclose recombinant class I and II HLA molecules (for example see, abstract, paragraphs 0120-0122, para. 0200, para.0212). Hildebrand et al disclose that these molecules can be used in methods for the removal of anti-HLA antibodies (para.0120).

Hildebrand et al differ from the instant invention in failing to teach the step of contacting the sample and removing the bound anti-HLA antibodies. Hildebrand et al also fails to teach the sample is a serum sample.

Whitehead et al disclose methods for depleting a sample of a biological molecule of interest by contacting the sample with an immobilized bioaffinity adsorbent. Whitehead et al disclose that the bioaffinity adsorbent can be any biological or other molecule capable of specific or nonspecific binding or interaction with another biological molecule. Whitehead et al disclose that the analyte can be immobilized to a magnetic particle. (col 6). Whitehead et al disclose removing the bound biological molecule from the sample to deplete the sample.

DeVito et al disclose serum samples from patients comprise Anti-HLA antibodies and teach depleting these antibodies from the sample.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilize the recombinant HLA molecules as taught by Hildebrand et al on magnetic particles as taught by Whitehead et al and incorporate contacting and removing steps as taught by Whitehead et al because Hildebrand et al specifically teaches that these molecules can be used in methods of removing anti-HLA antibodies and Whitehead et al specifically teaches steps of removing a biological molecule from a sample and also teaches that the bioaffinity adsorbent can be any biological or other molecule capable of specific or nonspecific binding or interaction with another biological molecule.

It would have also been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a serum sample as taught by DeVito et al because DeVito et al shows that it is known in the art that serum samples comprise anti-HLA antibodies.

14. Claims 35 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Devito et al in view of Walter et al or Barnardo et al and further in view of Whitehead et al (US 4,554,088).

See above for the teachings of Devito et al., Walter et al., and Barnardo et al.

Devito et al., Walter et al., and Barnardo et al differ from the instant invention in failing to teach the solid support is magnetic beads.

Whitehead et al teach magnetic beads coupled to biological molecules. Whitehead et al teach that the magnetic particles can be used in systems in which the separation of certain molecules from a surrounding medium is desired. Whitehead et al teach that the magnetic particles provide for magnetic separation in biological systems as an alternative to centrifugation (used by Devito) (col 2). Whitehead et al disclose that the particles can be dispersed in aqueous media without rapid gravitational settling and conveniently reclaimed from the media with a magnetic field (col 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate magnetic particles as taught by Whitehead into the modified method of Devito et al because Whitehead et al shows that the magnetic particles provide for magnetic separation in biological systems as an alternative to centrifugation (used by Devito) and also shows that the particles can be dispersed in aqueous media without rapid gravitational settling and conveniently reclaimed from the media with a magnetic field.

Response to Arguments

15. Applicant's arguments filed April 21,2006 have been fully considered but are moot in view of the new ground(s) of rejection.

Conclusion

16. No claims are allowed.

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Rhode et al (US 6,232,445) disclose recombinant MHC class II molecules (abstract, col. 12).

Frayser et al., (Empty and Peptide-Loaded Class II Major Histocompatibility Complex Proteins Produced by Expression in Escherichia coli and Folding in Vitro, Protein Expression and Purification 15, 105-114, 1999). Frayser et al disclose HLA-DR1 expressed in E-coli.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1641
June 22, 2006

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